HUMAN DRUG CGMP NOTES

(Volume 1, Number 2)

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(A Newsletter on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals)

Issued By: **The Division of Manufacturing and Product Quality, HFD-320**
Office of Compliance
Center for Drug Evaluation and Research

Editor: Paul J. Motise, HFD-323
Circulation Manager: Gayle Dolecek, HFD-323

IN THIS ISSUE:

NOTE FROM THE DIVISION DIRECTOR:

First, thanks for your feedback regarding the first edition of HUMAN DRUG CGMP NOTES. Paul Motise (Editor) and the rest of the gang have put a lot of work into this project ... and, from your reaction, it has paid off. We, too, are excited at the prospects for enhancing communications in this dynamic area. We hope this second edition

is as helpful.

Our objectives are clarity, timeliness, and focus on the issues most important to you. Therefore, your comments on format, content, and items of interest are absolutely essential. Please don't be shy. Again thanks for your interest and support.

Paul Vogel

EDITOR'S NOTEBOOK:

This is the second issue of a periodic newsletter on CGMPs for human use pharmaceuticals. I am pleased that our first edition was so well received (look for the newsletter to appear regularly on the FDA CD-ROM disk, published by SAN-DO's Steve Kendall). The purpose of the newsletter is to enhance field/headquarters communications on CGMP policy issues and to do so in a timely manner. We hope to use this document as a forum to hear and address your CGMP policy questions, to let you know what CGMP projects are in the works so you may respond to industry inquiries as to "what's cooking", to provide you with inspectional and compliance points to consider that will hopefully be of value to your day to day activities, and to clarify existing policy and enforcement documents.

Each issue of HUMAN DRUG CGMP NOTES will be published as needed. We wish to stress that this newsletter is intended to supplement, not supplant existing policy development/issuance mechanisms. HUMAN DRUG CGMP NOTES will provide a fast means of distributing interim policy and addressing questions.

Starting with this issue, we've made some improvements: a division contact list, *FAX FEEDBACK*, and E-mail distribution, as explained below. We value your suggestions for more enhancements.

We need your feedback for this publication to be helpful to your day to day inspectional and compliance activities. Furthermore, because wide input makes for more robust policy making, we'd appreciate your criticisms, suggestions and comments. Therefore, appended to each newsletter will be a *FAX FEEDBACK* sheet to make it easier for us to communicate. In addition to FAX (at 301-295-8202), you can reach the Policy and Guidance Branch, HFD-323, by interoffice paper mail, using the above address, by phone at (301) 295-8089, or by VAX electronic mail at BARR::A1::FDACD, or MOTISE::A1::FDACD.

Speaking of electronic mail, if you would like to receive an electronic edition of the newsletter via electronic mail, let us know (see the check off line in FAX FEEDBACK).

Finally, we're including an up to date listing of division contacts by subject area, so you'll know who to call on specific topics.

Thanks!

Paul J. Motise

POLICY QUESTIONS:

How many and, what size, pilot stability batches for ANDA/NDA (non-antibiotics) Pre-Approval Inspections do we expect?

References: See 21 CFR ∋ 211.166 (Stability testing), and Office of Generic Drugs Policy and Procedure Guide #22-90.

An exhibition batch (used to generate bioequivalence and stability data) must be representative of the product to be marketed. For ANDAs the batch is compared to the innovator's product -- the NDA exhibition batch is compared to the product used in pivotal clinical trials.

Generally, only one exhibition batch need be made.

We expect the exhibition batch to be made in accordance with CGMPs, using equipment, processes, procedures the same as, or equivalent to, what is anticipated for commercial batches.

Size? The exhibition batch should be at least 10% of the proposed production batch, or at least (for sold dosage forms) 100,000 dosage units, whichever is greater.

Division Contact for Further Info: Bruce W. Hartman, CSO, HFD-324, (301-295-8098).

Is Retrospective Validation an acceptable correction to no validation for a computer system used to control a manufacturing process?

References: See 21 CFR 211.100, and the Guideline on General Principles of Process Validation.

Yes! This question came up at a recent conference of FDA National Experts. A firm purchased and used a computer program to control a manufacturing process but failed to validate it. Such a program must be validated because it is an extension of the manufacturing process itself and generally embodies portions of what must be in a master production record.

The firm responded to the inspectional observation by saying it would conduct retrospective validation. Although at this point the firm should have known to prospectively validate the program prior to using it, we would not refuse to evaluate retrospective validation as a corrective measure.

Retrospective validation in this instance, like any other post-shipment corrections to CGMP misdeeds, would not negate the adulteration charge applicable to the lots made under the unvalidated process. However, the need for regulatory action will depend on the circumstances, and should consider all factors that relate to product quality.

Division Contact for Further Info: Paul Motise, CSO, HFD-323, (301-295-8089).

Absent analytical methods, how can requirements for specific end product testing be met?

Reference: 21 CFR ∋ 211.165 (Testing and release for distribution)

Strictly speaking, they can't! Discretion and emphasis on production controls/available pre-dosage form tests come into play.

For most drug products analytical methods exist to determine potency and identity of the active ingredient in the final dosage form. However, some products contain active ingredients (e.g., oleaginous substances such as mineral oils, petrolatum and waxes) for which assay procedures or identity tests don't exist. What then?

We will exercise discretion regarding enforcement actions where analytical testing methods are not reasonably capable of being performed. Needed are the manufacturer's good faith efforts at developing suitable methods to determine active ingredient strength/identity in the dosage form, and the demonstration to our satisfaction that such methods are not feasible using current scientific techniques.

In these cases other CGMP controls merit additional inspectional attention. Taking on added importance are:

(1) component testing/release (∋ 211.84) using compendial and/or other suitable tests to assure ingredient conformance to specifications before release for production;

(2) in-process controls (e.g., §§ 211.101, 211.110, 211.186 and 211.188) to ensure that the correct amounts of ingredients are used and that the manufacturing process is under control; and,

(3) dosage form conformance to appropriately established specifications (e.g., physical characteristics) that can be determined by testing.

Division Contact: William Crabbs, CSO, HFD-323, (301-295-8089)

Warehouse drug storage temperatures, what's objectionable?

Reference: 21 CFR § 211.142 (Warehousing procedures)

Detrimental temperatures are objectionable, not brief "spikes".

CGMPs require that warehouse storage conditions of temperature, humidity and light do not adversely affect drug product strength, quality, and purity. Brief "spikes" in temperature or other interludes of adverse conditions may not necessarily impact product quality, and, in fact, may be expected from time to time in the "real world".

In assessing the significance of adverse storage conditions, such as elevated temperatures, be sure to consider all the circumstances that influence whether or not the storage conditions you encounter are likely to be detrimental to the product. Evaluate, for example, the duration and extent of the temperature excursion, the complexity of drug product packaging (cartons within cartons) and their attendant insulating affect, labeled storage condition statements, and time remaining on labeled expiration dates.

Division Contact: Paul Motise, CSO, HFD-323, (301-295-8089)

Can recycled plastics be used for drug product containers?

Reference: 21 CFR § 211.94 Drug product containers and closures.

Although there's no prohibition, the need for batch to batch uniformity/purity makes such use difficult at best.

We've received several inquiries on plastics recycling, particularly where using recycled plastics may have been accepted for foods. CGMPs dictate that drug product containers/closures not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality, or purity of drug products beyond established requirements. Containers/closures must also provide adequate protection against foreseeable external factors in storage/use that could deteriorate or contaminate the product. Wide variance in product specifications, chemistry and stability make assessment of container/closure suitability a product by product affair.

Batch to batch uniformity of materials that make up container/closures is vital to assure product compatibility and general container suitability for each lot of drug product. Recycled plastics could be used for drug container/closures if a firm could validate the batch to batch consistency and specifications conformance for recycled materials. However, attaining such consistency and quality from "regenerated post-consumer" [watch for this new buzz phrase] plastic -- stuff of dubious and diverse origin -- is difficult at best.

Regarding food use acceptability, FDA determination that a given plastic may be acceptable for food packaging doesn't necessarily mean that the material is acceptable for drug packaging as well.

We are unaware of any drug manufacturers that are using, or have applied in NDAs/ANDAs for

use of, recycled plastics. However, be aware during your inspections that the issue may arise, especially in light of the growing popularity of recycling, in general. Be sure to report any instances where recycled plastics are used.

Division Contact: Paul Motise, CSO, HFD-323, (301-295-8089)

POLICY EMERGING:

Item: Metrification of Federal Standard 209E (Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones, 9/11/92)

Revised Federal Standard 209(e) includes metrification of units of measurement. The document serves as a transition from English to Metric units, so both types are presented. Metric units are preferred.

The switch from English to Metric as a means of expressing particulate air quality entails some precision of conversion and sampling point differences such that it is not acceptable to qualifying a clean room in Metric units by performing a mathematical conversion of the English values.

However, we would accept for trending purposes only, mathematical conversion of the old English system data into metric units until a sufficient data base has been established to use "pure" metric data.

Our position is that a facility that has been properly certified, qualified, or validated at a class in the English system need not re-qualify the facility in Metric terms to remain in compliance. The degree of cleanliness, in the English system would remain acceptable. Re-qualification in the Metric system may be delayed until it would otherwise have been scheduled or required.

Division Contact: Robert Sorensen, CSO, HFD-322, (301-295-8095)

Solid Oral Dosage Forms: Blend Uniformity Acceptance Criteria

Blend uniformity validation includes setting appropriate acceptance criteria for, and limits on acceptable variation in, assay results. Limits for blend sample assays should be appropriate for the product in question and should provide assurance that the finished product will meet established specifications. When setting these limits, firms should consider their historical data on blend uniformity achievable with their equipment. Finished product compendial assay limits would be appropriate for blend validation purposes.

Most firms should be able to demonstrate blend assay results well within compendial assay limits, typically 90 to 110% of label claim. However, a firm should use narrower limits (e.g., 95 to 105%, or 98 to 102%) where its historical data shows the capability of meeting those limits. Similarly, firms using sensitive and reliable analytical methods should be able to obtain relative standard deviations (RSDs) or coefficients of variation of 4 to 5% on blend sample results.

It is inappropriate to apply the USP Uniformity of Dosage Unit (Content Uniformity Test or CUT) criteria (85 to 115% of label claim and RSDs of 6 to 7.8) to a blend validation study for the following reasons:

1. Blending is only one step in the manufacturing process and allowances must be made for the impact of other processing steps on finished product uniformity. For example, agitation of blended material during transport or prolonged storage could cause demixing. Similarly, vibration of some bulk blended material in feed hoppers (for compression or encapsulation equipment) may demix the blend, thus increasing the variability in the finished dosage unit.

2. Blend assay results of 85 to 90% of label

would not provide any assurance that the finished product will be satisfactory, but would meet USP CUT limits. Similarly, blend sample results ranging from 85 to 115% of label claim, would appear to show that the blend is non-uniform.

Keep in mind that setting inappropriate limits and obtaining unacceptable results are not equally significant. Inappropriately wide limits are of lesser significance if a firm consistently achieves much narrower assay results. For example, if a firm establishes limits of 85 to 115% but obtains blend results of 95 to 105% or better, the limits are objectionable but of less regulatory significance than if some of the results fell outside of the 90 to 110% range.

Generally, with all other factors being equal, CGMP discrepancies with regard to blend uniformity would be less significant for a high dose drug of moderate therapeutic significance (ibuprofen or acetaminophen, etc.) than for a low dose potent drug of high therapeutic significance and/or a narrow therapeutic range such as warfarin tablets. Narrow therapeutic range drugs are those where the difference between a non-effective dose and a toxic dose is small. There is a list of narrow therapeutic range drugs as an appendix to the Compliance Program for Pre-Approval Inspections.

Division Contacts: William Crabbs, HFD-323, (Phone 295-8089), and Tony Lord, HFD-325, (Phone 295-8098).

IN THE WORKS:

In the last issue of HUMAN DRUG CGMP NOTES we answered the following project status questions:

Bioretention sample regulation status?

Where are the revised CGMP labeling regulations?

Status of the third copy drug application regulations?

The Division of Regulatory Affairs (HFD-360) manages CDER's process of developing and issuing regulations specific to human pharmaceuticals. We work closely with Al Rothschild (Division Director) and his staff in the development of regulations dealing with CGMP, product quality, and preapproval program issues. His division advises us, as we go to press that:

The final rule on bioretention samples is scheduled for publication in the 4/28/93 Federal Register. The labeling and third copy regulations are under review at the Office of Management and Budget (OMB). We will keep you posted as to further federal register notices on these items. Stay tuned.

In the last newsletter edition we also gave a background on:

Electronic Signatures and Electronic Records, what's in store?

Progress has been made in this area, as well. A draft proposed regulation on electronic records and electronic signatures, a rule that would state conditions under which such electronic documents and endorsements would be acceptable in lieu of paper and handwritten signatures, in all FDA program areas, has begun the process of agency clearance. It is possible that the proposed rule will publish this summer in the federal register. Again, we'll keep you posted on this important project.

Guidelines and Inspectional Guides Under Development, Status Changes:

<u>Guide to Inspection of Solid Dosage Form Manufacturing:</u>

This document originally included guidance on validation as well as equipment, activities, and

terminology relevant to manufacture of capsule and tablet dosage forms. It has been decided to cull out and address validation in a separate guide, as noted below.

The draft of this guide has been finalized and forwarded to the Division of Field Investigations (HFC-130) for clearance/publication.

Division Contact for Further Info: Willaim Crabbs, CSO, HFD-323, (301-295-8089)

Guide to Inspection of Solid Oral Dosage Form Validation:

This document, initiated by Tony Lord, provides inspectional guidance on prospective validation of the manufacture of solid oral dosage forms. The information in this guide had originally been included in the Guide to Inspection of Solid Oral Dosage Form Drug Manufacturing, but has been separated to form this document.

The draft of this guide has been finalized and forwarded to the Division of Field Investigations (HFC-130) for clearance/publication.

Division Contact for Further Info: William Crabbs, CSO, HFD-323, (301-295-8089)

Guide to Inspection of the Small-Scale Production of Liquid Injectable Radiopharmaceutical Drug Products Used in Positron Emission Tomography (PET):

This guide, initiated by HFD-322, addresses manufacturing processes and controls appropriate for PET Centers engaged in small-scale production. PET radiopharmaceuticals (e.g., Fludeoxyglucose F 18 Injection, USP) have extremely short half lives. Their biological distribution in the body is followed by a positron tomograph, or "PET scanner", which detects photons emitted as a result of the radioactive decay of the PET agent. These dosage forms are usually intended for injection or inhalation. PET Centers are typically associated with hospitals or other similar medical centers, where the complete cycle from manufacture through administration to the patient is completed within a matter of hours. The manufacturing sequence includes the bombardment of a target material with charged particles originated in a cyclotron, a complex sequence of computer-controlled steps for the synthesis of the drug substance, sterilizing filtration, and aseptic filling. One batch typically consists of one multiple dose vial. The specific manner in which CGMP would apply to the unique PET operations vary significantly from what is normally expected with conventional sterile drug manufacturing. We expect that in the future more PET Centers will arise upon approval of a pending NDA.

The draft guide was forwarded to the Division of Field Investigations for clearance/publication.

Division Contact for Further Info: John Levchuk, Ph.D., CSO, HFD-322 (301-295-8095).

Guideline on Supplements to NDA's/ANDA's for Non-Sterile Products:

This guideline provides information on practices and procedures for notifying FDA of changes in approved drug product applications. The document further defines the requirements in 21 CFR Section 314.70 for manufacturing changes that need to be submitted as a pre-approval supplement and those that fall within the scope of the CGMP regulations and only need to be described in the annual report. Guidance is provided in three specific areas: changes in equipment; reprocessing of drug products that fail to meet specifications; and changes made to the physical facility.

A draft has been forwarded to the Division of Regulatory Affairs for coordination and publication of a federal register notice of availability for public comment.

Division Contact: Gayle Dolecek, CSO, HFD-

323, Phone 295-8089.

P. Motise 4/27/93
DOC ID CNOTESC.593

DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
SUBJECT CONTACTS

(Note: All phone numbers are in area code 301, unless otherwise noted.)

Applications Integrity Policy	Bradford Williams	295-8098
Aseptic Processing	John W. Levchuck	295-8095
	Robert L. Sorensen	"
	Edwin Rivera	"
Bulk Drugs	Bill Crabbs	295-8089
	Tony Lord	295-8098
CGMP Guidelines	Paul Motise	295-8089
Civil Litigation Guidance:		
Non-Sterile	Bradford Williams	295-8098
Sterile	Terry E. Munson	295-8095
Clinical Supplies	Paul Motise	295-8089
Computer Validation	Paul Motise	295-8089
Content Uniformity	Tony Lord	295-8098
Criminal Litigation Support	Sally Schrivener	295-8054
	Nick Buhay	(401) 962-0873
Data (Application) Integrity	Tony Lord	295-8098
	Bruce Hartman	"
Dissolution	John Dietrick	295-8098
Electronic Records/Signatures	Paul Motise	295-8089
Foreign Drug EIs (Compliance)	Jerry Kirk	295-8089
Labeling Controls (CGMPs)	Tony Lord	295-8098
Laboratory Issues	Bradford Williams	295-8098
LAL/Pyrogens	Terry Munson	295-8095
Medical Gases	Duane S. Sylvia	295-8095
Microbiological Issues	Terry Munson	295-8095

DIVISION OF MANUFACTURING AND PRODUCT QUALITY, HFD-320
SUBJECT CONTACTS (Continued)

NDA/ANDA Pre-Approval Inspections	Bruce Hartman	295-8098
Particulates in Parenterals	Duane S. Sylvia	295-8095
Penicillin Cross Contamination	Duane S. Sylvia	295-8095
PET Radiopharmaceuticals (CGMPs)	John Levchuk	295-8095
Process Validation (Non-Sterile Dosage Forms)	John Dietrick	295-8098
Process Validation (General)	Paul Motise	295-8089
	Bill Crabbs	"
Repackaging	Gayle Dolecek	295-8089
Salvaging	Paul Motise	295-8089
Stability/Expiration Dates	Barry Rothman	295-8098
Sterile Facility Construction (Clean Rooms)	Robert Sorensen	295-8095
Sterilization Validation	John W. Levchuck	295-8095
	Robert Sorensen	"
	Edwin Rivera	"
Supplements	Gayle Dolecek	295-8089
Tamper-Resistant Packaging	Duane S. Sylvia	295-8095
Water Systems	Terry E. Munson	295-8095

FAX FEEDBACK

TO: Editor, HUMAN DRUG CGMP NOTES, HFD-320
FAX: 301-295-8202 (Phone 301-295-8089)

FROM: _____

AT: _____ MAIL CODE: _____

PHONE: _____ FAX: _____

E-MAIL ADDRESS: _____
To receive the electronic edition of HUMAN DRUG CGMP NOTES via E-mail, check here _____.

This FAX consists of this page plus _____ page(s).

I found this issue of HUMAN DRUG CGMP NOTES to be [check as appropriate]:

__not very; __ somewhat; __ very; __ extremely informative, and

__not very: __ somewhat; __ very; __ extremely useful to my inspectional/compliance activities.

Please have the HFD-320 information contact person get in touch with me regarding:

Pilot Stability Batches ___ Recycled Plastics ____
Retrospective Validation ___ Metrics and 209E ___
End Product Testing ___ Blend Uniformity Criteria ___
Warehouse Storage Temps ___ Others:
_____

Future editions of the newsletter should address the following CGMP questions/issues:
_____
_____
_____